

(This copy of Dr. Siegel's Warning Letter response has been annotated in BOLD italics in parentheses with FDA's analysis/response to each issue discussed.)

June 14, 2004

Timothy A. Ulatowski, Director
Office of Compliance
Center for Devices and Radiological Health
Food and Drug Administration
2094 Gaither Road, Rockville, Maryland 20850

RE: RESPONSE TO FDA Warning Letter dated May 27, 2004

STUDY: "[REDACTED]

", at Study Site [REDACTED]

SPONSOR: [REDACTED]

Dear Mr. Ulatowski:

Thank you for the opportunity to respond to your Warning Letter, which you issued on May 27, 2004. We would like to note that this Warning Letter, in large part, relates to information that we discovered via an internal audit and voluntarily disclosed to the Sponsor and to you, the FDA.

We have supplied a detailed response on a point-by-point basis, so that you might take the opportunity to reconsider the issues and rescind the letter. With that in mind, we would like to share some background information, to assist in your analysis and deliberations.

BACKGROUND

Advanced Cardiac Specialists ("ACS") has successfully conducted dozens of clinical trials over the past ten years. ACS has a staff of experienced employees who are assigned to the research department. At present there are seven full time employees, including a full time research physician. ACS employees have authored dozens of articles in internationally-indexed publications as a result of this research, which has provided an invaluable service to the medical community.

In October 1999, we agreed to conduct a research trial on the [REDACTED]. The protocol for this trial provided at that time, was ambiguous. Conversations with the Sponsor clarified a number of ambiguities in the reporting responsibilities, at the initiation of enrollment of patients in this trial. We understood our reporting responsibilities and performed them appropriately.

One of our employees, who will be anonymously referred to as John Doe, had been working in research for over eight years without incident. Mr. Doe was a good employee, and received favorable performance reviews each year. In September 2001, John Doe was assigned as Clinical Research Coordinator ("CRC") for this trial. As this trial was reaching its conclusion in late 2003, consistent with our routine procedures, a brief review of the file was conducted. In December 2003, our Medical Director of Research ("MDR") and our

Research Director ("RD") became aware of circumstances that led them to believe that Mr. Doe's compilation of files for this trial were not in proper order. Based upon this concern, Mr. Doe was immediately suspended from all further file responsibility, and put on paid administrative leave. Mr. Doe was not allowed any further access to the files. Our MDR and RD immediately began a comprehensive internal audit of this trial. The Sponsor was also notified at that time so that all parties were aware of a potential problem.

The results of this audit suggested that there were several documents that had been falsified by the CRC. Mr. Doe denied that the documents had been falsified. When queried further, he could not provide any explanation or corroborative evidence as to the source of the information that was included in the forms. We also could not confirm the veracity of his information via the use of "primary source documents". Based upon these findings, Mr. Doe was terminated. Mr. Doe was not allowed any further access to any records from the date of suspension, in order to maintain integrity of the records.

An exhaustive audit was then performed on each of the enrolled patient's research file. This included all information from the enrollment date to date of the audit, including information that predated Mr. Doe's involvement as CRC. Special attention was paid to the clinical course of the patients participating in the trial to ensure that no patient safety issues were involved. *No patient safety issues were discovered.*

If the data could not be corroborated by "primary source documents", it was withdrawn from the official submitted information for the study and placed in a separate file. We discerned that only information that met this unusually high standard of authenticity was safe and accurate for submission to the Sponsor, and ultimately to the FDA. We cannot say for certain that all of the withdrawn information was inaccurate or tainted. However, considering the situation, if the data did not meet the unusual high standard of verification by "primary source documents", they were labeled by us as having questionable authenticity, and were withdrawn. Hence, we presented only that information in each patient's research file that was verified in such a manner. We felt, under the circumstances, that this was an appropriate course of action, so that there would be no question about the information that was being submitted as part of the patient's official research file.

This audit was performed prior to any knowledge of the forthcoming FDA audit. On the advice of the District Office, the FDA auditor also confirmed independently during his review, that we had begun our internal audit without such knowledge.

The withdrawn information was never withheld or concealed, but was placed in a separate physical file for review by the sponsor and, later, the FDA. This appears to be the source of some confusion on your part. For instance, many of the deficiencies that are noted in your Warning Letter are based upon errors and/or alterations that were discovered by us, in our auditing process and presented to your auditor prior to the initiation of his audit. As these items could not be verified by "primary source documents" they were withdrawn, even before the FDA auditor's review of the documents and before your review of the documents in your office. They should not be the source of deficiencies attributed to our work, in your Warning Letter.

Based upon our audit findings, we believe that the employee's misconduct was confined to a narrow window of time at the end of 2003. We know of no confirmed reason as to the sudden change in Mr. Doe's performance, but we understand that he was undergoing some

personal and financial problems around that time. We also have no reason to believe that all of the withdrawn, uncorroborated data compiled by Mr. Doe is false. However, in an abundance of caution, anything less than information that was confirmed by “primary source documents”, was withdrawn.

(FDA disagrees. This was an on-going problem over at least two years. The questionable records dated back to at least January 2002, and the questionable SAE forms dated back to September 2001. Dr. Siegel’s own list of “withdrawn documents” covered a range from March 2001 through October 2003.)

We cannot emphasize strongly enough that this discovery was the result of our own internal audit. We took immediate action against the employee, to make sure that the files were protected, and to maintain the integrity of the research process and data. The Sponsor was contacted frequently during the audit process and kept apprised of our findings.

Prior to Mr. Johnson, the FDA auditor’s arrival at our office for a routine audit, the MDR and the RD were instructed to voluntarily disclose the problem we had discovered, and to point out the problems with some of the documents that could not be independently corroborated. **We emphasized that the withdrawn information should not be relied upon as part of the patient’s official research file, but was nevertheless being made available for review. We believe that having this extra set of withdrawn files may be part of the source of confusion that we perceive in your Warning Letter.** We believe that appropriate explanation was provided before the audit commenced, so that Mr. Johnson was aware of these issues. The information contained in each patient’s file is quite complex, and some of the documents withdrawn would not have been identified as being uncorroborated, without a high level of familiarity with the technical aspects of these procedures. Mr. Johnson was appreciative of our efforts, and acknowledged our assistance in navigating each of the withdrawn documents. No documents were withheld from Mr. Johnson, and he was also provided with access to our internal memos regarding our findings from the internal audit.

(FDA disagrees. “Withdrawing” the information from the patients’ records does not erase the fact that these issues occurred due to lack of Dr. Siegel’s oversight as the Clinical Investigator/CI.)

The data that was ultimately submitted regarding the clinical trials was 100% verified by “primary source documents” and, as you can see, showed that patient safety was never at issue. We believe that the data provided was sufficient for the evaluation of the device being tested. It is our understanding that the Sponsor has accepted this data from our site, and will be including it in the final IDE submission to the FDA.

(FDA disagrees. It is not for Dr. Siegel as the CI to decide if the data submitted was “sufficient for the evaluation of the device”. The CI is required to follow the study protocol and investigational plan as written.)

The Warning Letter does not appear to acknowledge the independent measures taken by my staff and me to identify, investigate, and correct these issues. The Warning Letter suggests that the withdrawn documents were part of the patient’s research file. The withdrawn documents were never intended to be part of the file that would be used by the FDA to make

its final determination regarding this device and should have been handled separately by ACS, the Sponsor and you, the FDA.

(FDA disagrees. Despite Dr. Siegel's statement that he did not intend the "withdrawn documents" to be part of the patients' files or part of the data used by the FDA in its evaluation, the fact remains that these are still source records, even if they were questionable. By deleting the records, he created huge gaps in the patients' study files which therefore resulted in a large percentage of protocol-required procedures and visits that were essentially not done. In addition, despite Dr. Siegel's assertion that these "withdrawn" records were not intended to be used as part of the FDA submission, the data was already submitted by the sponsor prior to Dr. Siegel's discovery of the problems. For example, 9-month end-point data on patients [REDACTED] and [REDACTED] were "withdrawn", but are in the sponsor's data listings. Adverse events for patients [REDACTED], [REDACTED], and [REDACTED] were also "withdrawn" but still appear in the sponsor's data listings.)

The following is a response to your allegations contained in the Warning Letter.

FDA Observation (shown in bold)

Failure to conduct the investigation in accordance with the signed agreement with the sponsor and the investigational plan [21 CFR 812.110(b)]:

Numerous deviations from the investigational plan occurred during the conduct of the study at your site. For example:

1) At least 10 Serious Adverse Events experienced by the study subjects were not reported to the study sponsor as required by the study protocol:

Advanced Cardiac Specialists (ACS) Response

We disagree.

This allegation appears to be inconsistent with the study protocol requirements. The Sponsor's study protocol had very limited "reporting requirements". Please see Attachment 2 titled "Reporting Responsibilities" (Table 5 of study protocol). The primary reporting requirements are for "unanticipated adverse device effects" and "deviations from investigational plan." The protocol does did not contain any specific requirements for reporting serious adverse events ("SAEs") to the Sponsor, that were not directly related to the device. This is likely because the protocol stated "There are no long-term safety issues with [REDACTED]. Major complications occur within the first 30 days" (see page 21 of study protocol).

Since this is not the norm with most research protocols, at the initial enrollment of patients in the trial, we sought a clarification regarding this very issue. In response, the Sponsor clarified that, in addition to the *Reporting Responsibilities* enumerated in Table 5 of the protocol, complications involving the [REDACTED], [REDACTED] procedure, [REDACTED] [REDACTED] related complications need only be documented in the CRF and they would be monitored and collected during the course of the trial by the Sponsor. (Please see Attachment 3 titled "Memorandum RE: Reporting Complications" dated January 30, 2004.)

Thus, “relevant” complications were routinely entered on the “Complication Form” in the e-CRF / CRF and monitored at the next visit. All complications were, however, submitted to the IRB if they met the independent criteria for reporting to the IRB, irrespective of whether they needed to be reported to the Sponsor.

The SAEs identified in the Warning Letter do not meet the criteria for reporting to the Sponsor, separate from the e-CRF. We complied with our responsibilities as noted in the protocol.

(FDA disagrees. According to a memo dated 1/30/04, titled “Clarification Regarding the Reporting of Complications” and signed by Dr. Siegel, adverse events to be reported to the sponsor included not just device-related events, but also “cardiovascular and vascular related complications.”)

- Pt. [REDACTED]: “Death” – [REDACTED]

Advanced Cardiac Specialists (ACS) Response

We disagree.

The patient [REDACTED] is not dead. He is alive and well. Patient [REDACTED] was last seen by an ACS physician for a 4-year follow-up visit on [REDACTED]/04.

To paraphrase Mark Twain, the news of this patient’s death has been greatly exaggerated.

Might we suggest that your letter probably intended to identify patient [REDACTED], who did expire on the date mentioned ([REDACTED]). If this is the case, we should note that this person expired some two years after the [REDACTED]. This was reported in compliance with the study protocol. Patient [REDACTED]’s death was entered on the Complication Form of the CRF and collected by the Sponsor during the monitoring visit in December 2003. *The patient’s death was unrelated to any complication from the device being tested.*

We believe that the clinical course and study documentation of both these patients ([REDACTED] and [REDACTED]) were handled correctly. We did not deviate from our responsibilities of this protocol. We would ask that this allegation be withdrawn.

(The patient referenced should be patient [REDACTED]. However, this event does not appear on the sponsor’s data line listings of adverse events dated 12/18/03 for patient [REDACTED].)

- Pt. [REDACTED]: “PTCA RCA (PDA)” – [REDACTED]

ACS Response

We disagree.

In compliance with study protocol, patient [REDACTED]'s [REDACTED] procedure was entered on the Complication Form of the CRF and collected by the Sponsor during the monitoring visit in December 2003. *This complication was unrelated to the device being tested.* It was noted and reported appropriately. We did not deviate from our responsibilities of this protocol. We would ask that this allegation be withdrawn.

(FDA disagrees. Even if Dr. Siegel feels this event was unrelated to the device, it was still a cardiovascular event and should have been reported. This event does not appear on the sponsor's data line listings for adverse events dated 12/18/03.)

- Pt. [REDACTED]:
 - "CHF" – [REDACTED]**ACS Response**

We disagree.

In compliance with study protocol, patient [REDACTED]'s hospital admission for worsening CHF was entered on the Complication Form of the CRF as required by protocol and collected by the Sponsor during the monitoring visit in December 2003. *This complication was unrelated to the device being tested.* It was noted and reported appropriately. We did not deviate from our responsibilities of the protocol. We would ask that this allegation be withdrawn.

(FDA disagrees. Even if Dr. Siegel feels this event was unrelated to the device, it was still a cardiovascular event and should have been reported. This event does not appear on the sponsor's data line listings for adverse events dated 12/18/03.)

- "DVT" – [REDACTED]
- ACS Response**

We disagree.

Per Sponsor's clarification, deep venous thrombosis was not considered a complication that needed to be documented / reported to the Sponsor. Hence, this was not done. However, an IRB submission of this event was performed in the usual manner and a copy of the submission should be in your possession for review. For your convenience, we have enclosed another copy of this IRB submission from our records (*Please see Attachment 4 dated 2/8/03*). *This complication was unrelated to the device being tested;* [REDACTED]. The event occurred almost two years after [REDACTED]. It was noted and reported appropriately. We did not deviate from our responsibilities of this protocol. We would ask that this allegation be withdrawn.

(FDA disagrees. Even if Dr. Siegel feels this event was unrelated to the device, it was still a cardiovascular event and should have been reported. This event does not appear on the sponsor's data line listings for adverse events dated 12/18/03.)

- Pt. [REDACTED]:
 - “PTCA with Stent” – [REDACTED]
 - “Right Renal Angioplasty” – [REDACTED]
 - “PTCA LAD” – [REDACTED]
 - “Pacemaker Implant” – [REDACTED]
 - “Bilateral Renal PTA” – [REDACTED]

ACS Response

We disagree.

In compliance with study protocol, each of patient [REDACTED]’s events enumerated above were entered on the Complication Form(s) of the CRF for review by the Sponsor during monitoring visits:

- PTCA with stent – the date was [REDACTED]. This was collected by the Sponsor during the monitoring visit in December 2003. *(FDA disagrees. The records do not support Dr. Siegel’s assertion. The site’s SAE report listed this event as occurring on 2/18/02, and reported to the sponsor by the study coordinator [REDACTED] on 2/27/02. This was one of the “withdrawn” documents, so it is questionable whether this record was actually submitted to the sponsor, or if it was created to make it appear as if it was. This AE does not appear in the sponsor’s data listings.)*
- Right Renal Angioplasty – [REDACTED]. This was collected by the Sponsor during the monitoring visit in December 2003.
- PTCA LAD – [REDACTED]. This was collected by the Sponsor during the monitoring visit in December 2003.
- Pacemaker Implant – [REDACTED]. This was collected by the Sponsor during the monitoring visit in December 2003.
- Bilateral Renal PTA – [REDACTED]. This is awaiting review by the Sponsor, pending monitoring visit.

These complications were unrelated to the device being tested. They were noted and reported appropriately. We did not deviate from our responsibilities of this protocol. We would ask that this allegation be withdrawn.

(FDA disagrees. Even if Dr. Siegel feels these events were unrelated to the device, they were still cardiovascular/vascular events and should have been reported. These events do not appear on the sponsor’s data line listings for adverse events dated 12/18/03.)

- Pt. [REDACTED]: “Worsening CHF” – [REDACTED]

ACS Response

We disagree.

This patient did not suffer from increasing CHF at any time during the course of the trial or even up to this day. His date of enrollment is [REDACTED]. His 2-year follow-up visit was done on [REDACTED]. In this period, he has had two SAEs, both of which were reported to the IRB and the sponsor – (a) obstruction of the right SFA requiring PTA, on [REDACTED] and (b) PTA to the left SFA on [REDACTED]. Please see *Attachment 5a* (Page 3 of 3, titled “[REDACTED] SAE Event Log”) and *Attachment 5b* (progress note dated [REDACTED] by PCP stating clearly that the patient is stable from a cardiac standpoint).

(FDA disagrees. This is not supported by the records. The site’s Follow-up Visit Worksheet for this patient for the 2-year visit on [REDACTED] asked: “has the patient had any complications since the last visit?” The written response was “YES Worsening CHF.”)

We did not deviate from our responsibilities of this protocol. We would ask that this allegation be withdrawn.

2) At least seven of the 19 enrolled study subjects had one or more missed visits.

3) At least twelve of the 19 enrolled study subjects had one or more missed study procedures.

4) At least ten of the 19 enrolled study subjects had one or more study visits outside the protocol-defined visit windows.

ACS Response:

This is a combined response to allegations 2, 3, and 4 of the Warning Letter.

We disagree. We do not believe that this fairly describes what actually happened, or the reasons for any deviation.

As you are aware, it is difficult for any research trial to have 100% compliance with the Sponsor’s study test requirements. There are a number of reasons why a patient may have missed a visit or a follow-up procedure. Not all of those omissions are the fault of the provider. Your allegation that all of these omissions are our fault is unfounded.

There were some missed visits / procedures during the course of the trial. However, the figures presented in your letter are misleading unless looked at in their proper context:

- It must be emphasized that this was a study involving a [REDACTED], where the primary concern is [REDACTED]. [REDACTED] could be demonstrated by one of several different methods (in order of least specific to most specific): Subjective questionnaire (such as [REDACTED]), physical examination, [REDACTED], [REDACTED] or a [REDACTED]. The protocol suggests a series of responses and tests in a prescribed “window” of time. ***(FDA disagrees. The protocol does not suggest. It requires specific tests and procedures to be conducted at the study follow-up visits. Study visit windows are also specifically defined in the protocol with lists of the data that “will be collected at each follow-up visit.”)*** Since we were obligated to withdraw data that was not confirmed by “primary source documents” and we were unable to turn back time, we

would obviously suffer the “holes” in our data collection that you describe in this section. As a substitute, we looked for substantive alternative tests to fill in the now obvious blanks. We did this by several different means. In some cases we brought the patients back for “repeat testing”. This led to protocol variance in some cases, and your subsequent charge of “out of window” testing / visits. We would object to being condemned for such a variance, since we were honestly attempting to repair the now discovered rent in our study.

(FDA disagrees. The fact that Dr. Siegel “withdrew data” due to questionable activities of his staff and replaced some with other data collected at later times does not excuse the fact that procedures required by the study protocol were not performed within the specified time-frames.)

- As stated earlier, due to irregularities detected in documentation by the study CRC, using extraordinary caution, in consultation with the Sponsor, a decision was made to withdraw all telephone visits conducted by the CRC, since the information obtained could not be corroborated with “primary source documents”. We hope that you would agree that telephone conversations, by their very nature, do not have “primary source documents” for corroboration. ***(FDA disagrees. Written phone logs are standard practice used by many study sites to provide documentation of information collected or discussed with study subjects over the telephone. A “primary source document” is generally described as the first place data is recorded, such as a telephone log.)*** Hence, with our discovery of the CRC’s poor work and our refusal to submit anything less than information verified by “primary source documents”, these data were appropriately withdrawn. This involved seven subjects in the study. This is, of course, the source of at least seven of the violations. I hope that you agree that these documents were necessarily withdrawn in order to repair the situation the best we could. I must emphasize that no inconsistency was detected; the visits were withdrawn only for lack of authentication. Wherever possible, follow-up visits were conducted for each patient in a timely manner, once we discovered the CRC’s poor behavior. This was the best option that we could manage.

(FDA disagrees. The protocol states that data should only be collected over the phone “as a last resort. This data will not be used to assess primary patency in support of a PMA application...all steps identified in section 2.10 need to be exhausted prior to resigning to telephone follow-up.” Section 2.10 of the protocol then states “efforts must be documented in the patient’s study file by copies of certified letters, phone logs, etc.” There is no indication that these steps were taken to contact patients for follow-up visits.)

- Similarly, four patients’ 2-year office visits were withdrawn for lack of supportive “primary source documents”. We think that it is not fair to now condemn us for the “holes” that will obviously be present in the place of “withdrawn” data. ***(FDA disagrees. Dr. Siegel chose to make “holes” by allowing questionable data to be withdrawn. However, the figures cited in the Warning Letter for missing data are based on the sponsor’s data listings for this site’s protocol deviations, and are not related to the site’s***

“withdrawn data.” If the “withdrawn data” was included, the numbers would have been much higher.)

- As in all protocols, some patients miss their appointments for a myriad of reasons (hospitalization; other illness; lack of transport; vacations, etc). For this group we simply completed appropriate deviation forms.
- To fulfill the scientific data requirements, most of the “missing data” patients were brought back and assessed [REDACTED] (clinical, [REDACTED], [REDACTED], [REDACTED]). Thus, many of the “out-of-window” visits were inevitable.
- [REDACTED] is usually associated with [REDACTED]. Associated clinical problems led to missed visits / procedures in patients who, for instance, had worsening angina ([REDACTED]), worsening COPD ([REDACTED]), lumbosacral neuropathy ([REDACTED]). As you know, all three patients did fit eligibility criteria at enrollment.
- As a corrective action, to improve compliance in future studies and to minimize deviations from protocol schedules in the future, a *Tracking Schedule* has been put in place. This and other corrective measures are discussed in detail towards the end of this response.

I would like to assure you that I fully appreciate my responsibilities as Principal Investigator in ensuring full compliance with the letter and spirit of every FDA-monitored clinical trial protocol that we participate in. Despite the unfortunate actions of a solitary member of my research staff, my research team and I made every effort to ensure that the scientific soundness of the trial and the rights, safety and welfare of the study subjects were preserved.

In this context, it is important to note that all 19 patients enrolled satisfied the stringent clinical and [REDACTED] eligibility criteria for the trial. The informed consent process involving these 19 patients was thoroughly scrutinized during the FDA audit and found to be correct and consistent in each of the study subjects. Technical success of the procedure was 95% (18/19 patients; one had [REDACTED]).

We believe that this allegation of wrongdoing is inaccurate, and unfairly penalizes us for the corrective action that was taken by us. We cannot be responsible for all missed visits or procedures. Nor can we say for sure that, given the unusual circumstances of this case, all of the withdrawn data was unreliable. If the withdrawn data were included (*and we are not suggesting that it should*), there would be significantly fewer instances of missed visits or procedures.

FDA Observation

Failure to maintain accurate and complete records for each subject enrolled into the study [21 CFR 812.140(a)]:

ACS Response

We disagree. We do not believe that this fairly describes what actually happened, or the reasons for any deviation.

The regulation you cite requires the participating investigator to maintain accurate, complete and current records relating to the investigation. As we stated above, as a result of our internal audit, only information that was verified by “primary source documents” was contained in the official research file reviewed by the auditor. The examples of wrongdoing all relate to documents that had been withdrawn, or documents that were corrected due to operator input error on a test performed upon the patient. These withdrawn documents were also provided to the auditor for separate review. Nothing was withheld from him. Unfortunately, this set of documents appears to be part of your misunderstanding and a source of our objections to your Warning Letter.

(FDA disagrees. The Warning Letter cite is correct. The records were not accurate and complete. By “withdrawing” documents, it made the study records even more incomplete. The regulations require accurate and complete records “of each subject’s case history and exposure to the device...all relevant observations, including records concerning adverse device effects [whether anticipated or unanticipated]).”

Numerous examples of study data inaccuracies and inconsistencies were observed in your study records. For example:

1) Study procedure documents have conflicting information:

- Pt. [REDACTED]: the [REDACTED] test record has the printed name of a subject with the initials “[REDACTED]” crossed out and the name of a subject with the initials “[REDACTED]” handwritten in. The printed date “[REDACTED]” is crossed out and “[REDACTED]” is written in. The record also notes this patient is 41 years old. Other study documents indicate this subject was [REDACTED] years old at the time.

ACS Response

We disagree.

This issue was addressed in great detail during the FDA site audit and clarified to the satisfaction of the FDA inspector.

- This alleged infraction appears to suggest that the [REDACTED] Form, which was printed contemporaneously with the performance of the test, should have been removed from the patient’s file. We do not believe that this action would comply with our obligations to the patient. The machine-produced test results were part of the patient’s file and must be included therein. To not properly label the test (albeit by handwritten method) seems inappropriate. The machine, because of operator error or otherwise, mistakenly printed the wrong name, patient age, and date of the test. The incorrect dates and patient names were cancelled and correct dates entered manually. *(Please see Attachment 6 titled “Memorandum RE: Demographic Inconsistencies in [REDACTED] Print-Outs at Gilbert Office” dated January 30, 2004).* The correction clearly eliminates the typewritten information. While the patient’s age was not corrected, we believe that, viewed in context with the rest of the information contained in the file, it provides accurate information.

(FDA disagrees. It is impossible to know whether the results printed under a specific patient's name and date actually pertain to a different patient and a different date. This results in highly questionable data. In addition, if the situation is as Dr. Siegel describes above, either he has improperly trained personnel working on the study, or his equipment is inadequate to properly conduct the study.)

- Attached is a copy of patient [REDACTED]'s "superbill" and a progress note for the date of test for this patient, which provides confirmation of the procedure being actually performed (*Attachments 7a and 7b*). The progress note of my nurse practitioner mentions the [REDACTED] which coincides with the value on the [REDACTED] test report.

(FDA disagrees. Dr. Siegel's attempt to justify this questionable record only adds another inconsistency. The superbill and the progress note referenced above described a test performed on 1/2/02. However, the suspect test record had a date of 1/7/02.)

- There was no inconsistent information on this test. This was noted and reported appropriately. We did not deviate from our responsibilities of this protocol. We would ask that this allegation be withdrawn.
- **Pt. [REDACTED]:** the [REDACTED] test record has the original printed name blacked out, with "[REDACTED]" written in. The date is also hand-written in as "[REDACTED]". The patient's age is given as 71; however, other study documents indicate this subject was [REDACTED] at the time.

ACS Response

We disagree.

This allegation is based upon a withdrawn document, which was not part of the patient's research file. Since this was withdrawn, it cannot possibly be the basis for any violation. Even then, as per protocol, the alternative option of a [REDACTED] was timely performed (*within window*) on the patient [REDACTED]. A copy of the report is included as *Attachment 8* titled "[REDACTED] Report" dated 1/21/02.

(FDA disagrees. The study protocol requires both segmental pressure tests and duplex ultrasound scan at the 9-month follow-up visit. They are not optional. This appears to be another case of an attempt to use another patient's report for a test that may not have been performed.)

This was noted and reported appropriately. We did not deviate from our responsibilities of this protocol. We would ask that this allegation be withdrawn.

- **Pt. [REDACTED]:** the 1-year [REDACTED] test records for [REDACTED] tests have the date 1/1/02 hand-written on them, with the patient's age listed as [REDACTED]. The 2-year [REDACTED] test records for the [REDACTED]

ACS Response

Once again, it would appear that comingling of the documents has happened. This allegation is based upon withdrawn documents, which were not part of the patient's research file. Since these documents were withdrawn they should not be the basis for any violation. Even then, as per protocol, the alternative option of a [REDACTED] [REDACTED] was performed on the patient to [REDACTED]. A copy of the report is attached as *Attachment 9a titled "[REDACTED] Report" dated 1/10/03.*

(FDA disagrees. The study protocol requires both segmental pressure tests and duplex ultrasound scan at the 9-month follow-up visit. They are not optional. This appears to be a case of an attempt to use one year's report for a test that may not have been performed the following year. In addition, the test reports noted above were each performed 2 months outside the protocol-specified window.)

- **Many photocopies of patient records that were machine-generated and should have had dates automatically printed on them at the time of testing have the dates inexplicably missing, while the original records were unable to be located.**

ACS Response

(FDA disagrees. “Withdrawing” the suspect documents does not eliminate the fact that they exist. All of these issues regarding the machine-generated pressure tests appear to suggest that there may have been attempts to use other information to substitute for procedures that were not done. This

warning letter cite was for inaccurate and incomplete study subject records, and these are but a few examples to support this.)

This was noted and reported appropriately. We did not deviate from our responsibilities of this protocol. We would ask that this allegation be withdrawn.

2) Subject records had conflicting information:

- **Pt. [REDACTED]:** an SAE for “Fem-Fem Bypass” that occurred on [REDACTED] was stamped “Faxed 9/27/01”, but the form itself was annotated “Revised 12/02”. Date of patient was listed as “[REDACTED]”.

ACS Response:

This allegation appears to be based upon confusion regarding the withdrawn documents. Records with inconsistent data were not included as part of the patient’s research file. This cannot support an allegation of wrongdoing, as these documents were appropriately withdrawn.

(FDA disagrees. This is one example of some inconsistencies in the records. Even though Dr. Siegel “withdrew” this record, it still appears on the sponsor’s data listings submitted to the FDA, so it was not withdrawn from the sponsor. Even if this event is accurately recorded here, the inconsistencies in the form date and the patient date indicate this record is questionable.)

We did not deviate from our responsibilities of this protocol. We would ask that this allegation be withdrawn.

Pt. 10418: an SAE for “PTCA w/Stent” that occurred [REDACTED] was stamped “Faxed 2/27/02”, but the form itself was annotated “Revised 12/02”.

ACS Response:

This allegation appears to be based upon confusion regarding the withdrawn documents. Records with inconsistent data were not included as part of the patient’s research file. This cannot support an allegation of wrongdoing, as these documents were appropriately withdrawn.

(FDA disagrees. This is another example of some inconsistencies in the records. Even though Dr. Siegel “withdrew” this record, it does not negate the fact that this adverse event, if it occurred, should have been reported to the sponsor.)

We did not deviate from our responsibilities of this protocol. We would ask that this allegation be withdrawn.

FDA Observation

Failure to adequately supervise the conduct of the study [21 CFR 812.110(c)]

- Your study records indicate that at least 14 of the 19 study subjects enrolled into the study had questionable and/or unverifiable data collected and reported to the study sponsor over a two or three year period by a member of your study staff.

ACS Response

- It is impossible to respond to this allegation for a number of reasons:
 - The federal regulation cited has no relation to the narrative.
 - You do not identify the patients involved.
 - Unverifiable data (such as telephone visits) are specifically permitted under the study protocol.
 - You do not identify any “questionable” data collected, so that a specific response can be provided.

(FDA disagrees. Dr. Siegel provided a document during the inspection titled “Detailed List of Withdrawn Documents”, which listed 14 subjects. The Federal Regulation cited is relative to the narrative in that this is one example of Dr. Siegel’s failure to adequately supervise the study, since so many patients were found to have questionable data.)

- The general allegation states that the Principal Investigator (PI) did not adequately supervise the conduct of the study and the research staff. Without specific facts where the other members of our research staff committed acts that were subject to inadequate supervision, no response can be provided. It is not reasonable to assume that the PI will supervise every act of all staff members at all times. Our internal audit was conducted in December 2003, and determined that John Doe’s misconduct was confined to a narrow period of time. We believe this allegation unfairly maligns ACS. I would like to direct your attention to *Attachment 10 titled “RE: FDA Audit of the [REDACTED]” dated February 11, 2004*. This was a memorandum written by our MDR to answer specific questions asked by Mr. Johnson during the audit. On Page 2 she attempts to give him “a timeframe in which John Doe’s work demonstrated inconsistencies”. During extensive discussions with at least 2 of the Sponsor’s monitors, they were very definitive about not having any major complaints with John Doe’s work until the last quarter of 2003.

(FDA disagrees. It is reasonable to assume the PI will supervise every act of staff members delegated study tasks, because it is required by Federal regulations. It is assumed that an investigator will delegate study tasks to persons qualified by training and/or experience to perform those tasks adequately. If an investigator cannot adequately supervise study personnel to ensure adherence to the investigational plan, the investigator is in violation of Federal regulations. The fact that the sponsor’s monitors had no complaints about the study coordinator’s work until the last quarter of 2003 does not mean these problems did not exist until then. As noted above, questionable records and “withdrawn” records date back to early 2001. It is possible that the monitoring at the time was inadequate to identify these issues. Regardless, it is still the PI’s obligation to ensure proper conduct of the study and adherence to the Federal regulations.)

- Data inconsistencies were detected during an internal audit and immediate and comprehensive actions were taken.
- Corrective measures were taken, which are described in detail toward the end of this response. *(Please see Attachment 12 titled “SOP Number 14: Quality Control”, version number 3.0, effective date 04/19/04).*

We did not deviate from our responsibilities of this protocol. We would ask that this allegation be withdrawn.

- **Some of the information involved primary safety and efficacy data that has already been reported to the FDA by the Sponsor.**

ACS Response

We disagree.

Patient safety and data regarding primary safety and efficacy were never compromised. As discussed above, the study protocol noted that the most significant risk occurs [REDACTED] (see page 21 of study protocol). None of the data in this time period can be questioned. The next threshold was at the nine-month level. Two patient files contained data at this time period which we could not verify against “primary source documents”; these documents were then appropriately withdrawn. As noted above, for those two patients, repeat separate studies were performed to verify [REDACTED]. Hence, primary safety and efficacy data were not compromised.

(FDA disagrees. As Dr. Siegel states above, two subjects had questionable 9-month data. Both of these subjects’ 9-month data appear in the sponsor’s data listings for efficacy.)

I would like to direct your attention to *Attachment 11 titled “RE: Internal Audit Findings” dated January 30, 2004, which includes “Detailed List of Withdrawn Documents”*. Most of the withdrawn documents are 3 or 4 year follow-up telephone visits (per protocol) which were withdrawn as a measure of abundant caution, since the telephone records would be more difficult to verify and, by their very nature, preclude being backed up by “primary source documents”. That did not mean that the information was inconsistent or false. It was simply withdrawn because it could not meet our higher standard of verification. *This data does not fall within the scope of primary safety and efficacy data.*

(FDA disagrees. As noted in the Attachment referenced above, of the 37 documents “withdrawn” by Dr. Siegel, only 14 are related to telephone follow-ups. The remaining 23 documents refer to office visits, procedures, and adverse events.)

We have also confirmed from a reliable official at the sponsor that the final IDE submission will include the **verified data** from our site (nearly 10% of total enrollment).

We did not deviate from our responsibilities of this protocol. We would ask that this allegation be withdrawn.

- **You signed Case Report Form submission forms on 9/13/03 for each of the 19 study subjects which state that you verified that all Case Report Forms for the study are accurate.**

ACS Response

This study used electronic CRFs. Per protocol, the primary CRC on the trial entered the data into the computer provided by the Sponsor. Data entry was a laborious process; the Sponsor trained him to do this task. Data was entered by him and periodically transferred via disk to the Sponsor. Until verified by the monitor, this data was considered “*unlocked data*”. Once the data had been monitored during a site visit by the (Sponsor’s) monitor and verified to be accurate, the data was “*locked*”. The first printout of the CRF records, obtained from the Sponsor in September 2003, contained only “locked data”.

In mid-September 2003, the Sponsor, for the first time, provided us with printouts of the electronic files for the patients in this study. We were asked to review nineteen notebooks, each of which contained over 100 pages of printouts of documents to review.

The supporting medical records were located in offices around the state. Based upon the limited time available, we relied upon the Sponsor’s providing data that it had independently verified, as well as data that had been entered by our staff, which we had no reason to question. I believe I acted reasonably under the circumstances. I also asked my staff to schedule this trial for an audit. When later informed that some of the data could not be supported by “primary source documents”, I directed that the data be withdrawn and notified the Sponsor. We cannot state that all withdrawn data cannot be properly included in this study. However, in an abundance of caution, the data has been withdrawn and was not intended to be relied upon, by the Sponsor or the FDA.

(FDA disagrees. A Clinical Investigator/CI cannot rely on the study sponsor or monitors to ensure that the study is conducted correctly, or that data is accurate and complete. Federal regulations are very specific as to the duties of CIs. If records are located in other offices around the state, it is difficult to see how Dr. Siegel could supervise the conduct of the study as the law requires. However, since he chose to conduct the study in this manner, it is expected that he will be held responsible for the integrity of the study data. Study sites must determine how they can ensure data integrity and protocol adherence throughout the entire conduct of the study [especially when conducted over several years], and not by merely auditing the study after its completion.)

To minimize the risk of any future re-occurrences, our procedures have been modified to require quarterly audits of the research files. (Please see Attachment 12 titled

“SOP Number 14: Quality Control”, version number 3.0, effective date 04/19/04). We will also request frequent and timely printouts from all sponsors using e-CRF formats.

- **As a Clinical Investigator, you must ensure that any staff or personnel who are delegated study tasks are appropriately qualified by training and/or education to correctly perform those tasks, and are adequately supervised by you to ensure conformance with the Investigational Plan.**

ACS Response

We agree.

We believe that our staff meets these guidelines. There is no indication that this is a training related issue.

We think it is pertinent to point out that the CRC involved in this case had been with the research department for nearly eight years and had been supervised and trained before she was ever given the status of primary CRC for any trial. *(Please see Attachment 10 titled “RE: FDA Audit of the [REDACTED]” dated February 11, 2004).* This is the first time we have ever encountered such a problem, something inconceivable to us before this incident. We are putting steps in place to ensure that such a problem does not occur again. The Standard Operating Procedure (SOP) #14 that relates to Quality Control has been revised *(with welcome inputs from sponsors, the FDA inspector and the District Office of the FDA in Los Angeles)* and is in the process of being implemented *(Please see Attachment 12 titled “SOP Number 14: Quality Control”, version number 3.0, effective date 04/19/04).*

- **You must also ensure that all study data and records are correctly collected and maintained.**

ACS Response

We agree.

It is our routine to collect and maintain data in a correct manner. In this study, we were, unfortunately, “submerged” by a rogue CRC, who had been a fine and trusted employee for over eight years. Still, we believe that our independent internal audit procedures successfully identified this problem. One might surmise that we were about 90 days too late in this case. To suggest such is not reasonable. One cannot imagine that any site might ferret out such a problem within only 90 days of the initiation of poor quality work by a trusted CRC. In fact, we feel fortunate indeed that we were able to sort out this problem in such a short timeframe. Thus, you might understand our consternation at the severity of the Warning Letter, considering our own self-motivated efforts.

(FDA disagrees. As noted above, the problems with the data integrity cover a period of over two years, from early 2001 through October 2003. The fact that the questionable data and the “withdrawn” documents cover such a wide time-frame calls into question the overall integrity of the entire study. Since the FDA

investigator did not audit all the patients' records, it is not possible to know if the examples used in the Warning Letter constitute all the issues with the study site, or if there are other problems that were not uncovered.)

More frequent and extensive audits should assist in maintaining compliance with this standard. We are hopeful that such a change will strengthen our checks and balances to minimize the chances of any re-occurrences. *(Please see Attachment 12 titled "SOP Number 14: Quality Control", version number 3.0, effective date 04/19/04).*

- **The data inconsistencies, unreported Adverse Events, and the unverifiable data collected by a member of your study staff raise serious questions as to the overall validity of the data generated during the conduct of this study at your site.**

ACS Response

We disagree.

The audited data submitted to the Sponsor is accurate and scientifically valid. The FDA inspector, Mr. Johnson satisfied himself on that count; the Sponsor has too. We were able to detect the problem, fix it, ensure the continued safety of patients, comply with our responsibilities to the Sponsor and fully assist and cooperate with the FDA to understand what happened here.

No Form-483 was issued at the completion of the audit by your inspector. The Sponsor is satisfied and has conveyed their intention to include our data in the Final IDE Submission.

There should be no doubts about the final data submitted by this site. We did not deviate from our responsibilities of this protocol.

Include supporting documentation of the specific steps you have taken or will take to correct these violations and prevent the recurrence of similar violations in current and future studies.

ACS Response

1. This entire experience has been uncomfortable and discouraging. We are also extremely saddened to witness the deterioration of a trusted CRC who has been with us for over eight years.
2. We are nevertheless implementing changes to improve our operations. Please see *Attachment 12 titled "SOP Number 14: Quality Control", version number 3.0, effective date 04/19/04*. Internal audits of study performance will be conducted on a quarterly basis for all active research studies. As part of our commitment to continuous quality improvements, SOP No. 14 has been revised to more clearly describe the responsibilities and procedures for conducting these internal audits. We received invaluable inputs from several sponsors, the FDA inspector and the Los Angeles District Office of the FDA. All research coordinators have been retrained on the

revised SOP. All providers involved in research activities at ACS are in the process of being retrained on the revised SOP, which became effective as of 4/19/04.

3. Please see *Attachment 13 titled "Quality Assurance Review – Case Report Form"*, version 01/28/04. This form will be utilized as part of the quarterly audit process.
4. To address the issue of missed visits, missed procedures and "out of window" visits, a *Tracking Schedule* is in the process of being set up for all patients enrolled in clinical research trials:
 - At enrollment, all patients will be immediately entered into a master log maintained by the office assistant in the research department, along with protocol-mandated schedules (tests required, blood draws, office visits and windows).
 - The office assistant will then schedule these procedures, enter them into the master log, and inform the appropriate CRC about the schedules.
 - The CRC may make changes to the scheduled dates to suit the convenience of the patient, *within the mandated "windows"*. Any such changes will be entered in the master log.
 - The office assistant will check the master log at the beginning of each month and make telephone reminders to patients to keep their scheduled appointments. Any last minute adjustments will be made at that time, again, *within the mandated "windows"*.
 - In case of a missed visit / procedure or an "out-of-window" visit, it will be brought to the attention of the RD or MDR, who will determine further action, in consultation with the PI.
5. As a proactive measure, we conducted a 100% audit of all other trials that John Doe had been working on concurrently during this trial. (*Please see Attachment 14 titled Internal Audit of Certain Clinical Trials Conducted at ACS, dated 5/11/2004*). The audits revealed no discrepancy in data collection. *The detailed audit findings were mailed to the FDA auditor, Mr. Johnson, as a voluntary follow-up measure from our site.*
6. As an additional proactive measure, we are in the process of conducting internal audits on clinical trials that did not involve John Doe as the primary CRC. Minor deficiencies were noted but no major inconsistencies have been found thus far.

Please provide a complete list of all clinical trials in which you have participated for the last five years.

ACS Response:

Please see *Attachment 15 titled "List of Clinical Trials, 1999-2004"* version 6/2004.

Conclusion

We do not, even for a moment, want to give the impression that we are justifying any of the inappropriate and unethical conduct of a member of our study team, or that our internal

controls are flawless. We have participated in over 100 FDA-monitored clinical research trials and fully understand the importance of clinical research. The validity of the scientific data we collect will determine if a new device or drug is safe for use by the global medical community in the future. We are part of a crucial decision-making process that impacts how medicine will be practiced all around the world. That is a serious responsibility and a unique privilege that we carry with pride.

Ours is a privately-owned practice. We receive no federal grants or subsidies to conduct research, unlike universities or larger institutions. We have lost money on our research activities in each of the last ten years. Our physicians accept this yearly revenue loss as part of our contribution to the community. We are involved in scientific activities because of a genuine and abiding interest in cardiovascular research.

In our own way, ours is a unique blend of clinical practice and science, outside the portals of formal university campuses, with a view to make state-of-the-art care available to the sickest patients as early as possible. Our commitment to the advancement of science is what distinguishes us from becoming “just another” for-profit clinical practice. Our reputation is hard-earned and dear to us, and our more than 40 providers all take a personal pride in our contributions to medical science.

A Warning Letter of the type and severity that you have issued to us will destroy the ability and effectiveness of our research team to take care of some of the sickest patients in the practice. We worry that indicting us after all our efforts to do the right thing, may cause the next site to hesitate against full and complete disclosure in a similar circumstance. Such concealment could only hurt the scientific community.

In this case, we believe that adequate supervisory efforts detected and corrected a flaw in the system in a timely manner, without compromising patient safety or primary safety and efficacy device data.

In the light of all this, we urge you to reconsider your position and withdraw your Warning Letter. We believe that if your Warning Letter is left to stand, it will effectively cause cessation of our research activities and cause us to abandon our efforts and the strong elements of our research program, created through ten years of hard work.

We believe that a withdrawal is especially appropriate, in light of the confusion between the documents contained in the research file and the withdrawn documents. We believe that the audit has pointed out some deficiencies and areas that could do well with improvement. We intend to work on these to improve our program. However, if your Warning Letter is not withdrawn, we believe that our program will not survive.

We assume that your intent is not to shut us down. We hope that a fair consideration of our response to the alleged deficiencies will lead you to conclude that the severity of the Warning Letter is unwarranted.

We understand that the request for withdrawal of a Warning Letter, once issued, is unusual. However, considering the facts and detailed documentation that we have laid before you, we urge you to consider withdrawing the Warning Letter.

We believe that withdrawal of the letter will allow us to preserve the scientific temper that has kept us among the top 100 cardiovascular programs in the country, with one of the lowest patient mortality and hospital-stay rates nation wide.

We thank you in advance for your consideration. Please feel free to call if you need any further information or clarifications.

Sincerely,

Robert M. Siegel, M.D.
Principal Investigator

Copy to:

1. Ms. Cynthia A. Harris, Consumer Safety Officer
Food and Drug Administration
Center for Devices and Radiological Health, Office of Compliance
Division of Bioresearch Monitoring, Program Enforcement Branch II
(HFZ-312)
2094 Gaither Road, Rockville, Maryland 20850
2. Alonza Cruse
District Director
Los Angeles District Office
Food and Drug Administration
19701 Fairchild
Irvine, CA 92612
3. Greg Lim, B.Sc., Phm, MHScHA, CIP
Director, Regulatory Affairs
Western Institutional Review Board
3535 Seventh Avenue SW
Olympia, Washington 98502
4. 